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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/858,016
Filing Date: May 15, 2001
Appellant(s): HIRSH ET AL.

Patrea Pabst
Registration No. 31,284
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed October 19, 2006 appealing from the Office action mailed April 19, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

GB 800,973	STERLING DRUG INC.	9-1958
DE 3338978	BASF AG	5-1984
3,898,323	FENNELL	8-1975
2001/0002999	NEUSER	6-2001

4,661,492	LEWIS	4-1987
5,686,112	LIEDTKE	11-1997
WO 00/35296	WRIGLEY	6-2000
5,310,561	JAO	5-1994
5,053,032	BARCLAY	10-1991
6,200,604	PANTHER	3-2001
6,863,901	HIRSH	3-2005

Remington's Pharmaceutical Sciences, 18th Ed. (1990), page 844.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(A) Claims 33-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claim 33 and independent claim 55 is directed to a second oral portion which is released for uptake in the intestine and wherein the second portion is either a sustained release or chewable formulation. It is unclear how the second oral portion is released in the intestine and yet is capable of being chewed. The examiner points out that the claim is directed to a sustained release or chewable formulation. If the composition is chewed then it cannot be released in the intestine as required by the claim. Further clarification is requested.

Claim 33, 41, and 55 respectively recite the limitation "the core". There is insufficient antecedent basis for this limitation in the claim.

Claim 37 recites the limitation "comprises one or more of the outer layers". There is insufficient antecedent basis for this limitation in the claim.

(B) Claims 33-39, 41-50, and 51-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over GB 800,973 in view of Powell et al (6,140,319) in further view of DE 3338978 in further view of Fennel et al (3,898,323).

GB teaches a multi-layered tablet comprising 1) an outer coating that contains a medicament that readily dissolves in the mouth 2) a signal layer containing a distinctive flavor, 3) an enteric layer around an inner layer comprising an oral medicament, and 4) a core that can also contain a medicament. See figure1 and claim 1 and 3. The outer coat is taught to readily dissolvable in the mouth. See column 2, lines 59-65. GB discloses that the enteric layer may be manipulated with a certain thickness to release the medicament in a given area or time, which is known in the art. See page 2. GB teaches that the tablet provides a means for dosing a patient with at least two separate medicaments, one of which is to be absorbed in the mouth and the other in the gastro-intestinal tract. See column 2, lines 47-59.

Example 1 teaches the immediate drug on the outside as N-isopropylarterenol (molecular weight 211.26) and the delayed core is theophyllin. Example 2 teaches an inner core comprising a drug and alginic acid (sustained release polymer) is coated with three coats of shellac and then an alarm layer is coated over this. The immediate layer comprising 10% nitroglycerin (molecular weight of 227.09) is dusted. The tablet is utilized to promptly treat angina followed by the delayed action of pentaerithrytol in the inner core. Optionally the outer medicament layer may

comprise the flavor components of the alarm layer. Note it is the examiner's position that the medicament core reads on chewable formulation since chewable does not impart any structure except that it must be capable of being chewed.

GB does not teach instant drugs as defined in independent claim.

Powell teaches vasopeptidase inhibitors to treat angina pectoris. Powell teaches the vasopeptidase inhibitor in combination with other active agents known to treat angina. These agents include nitroglycerin, instant verapamil hydrochloride, instant amlodipine, etc. See column 4, lines 5-15.

DE teaches the use of verapamil (taught as a cardiovascular agent) in the amount of 5-25mg in a sublingual or buccal tablet. See abstract.

Fennel teaches the process of a coating a core by tumbling the core in a drum containing the coating material or spray coating. Fennel teaches alternatively the coating may be applied over the tablet core by compressing the core with a tablet press. See column 3, lines 14-30.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to look to the teachings of Powell and utilize the instant verapamil in GB's nitroglycerin example. One would have been motivated to do so since Powell teaches that the prior art's nitroglycerin and instantly claimed drug verapamil are both utilized to treat angina. Thus, a skilled artisan would have been motivated to substitute nitroglycerin with verapamil with the expectation of similar results since GB teaches the use of nitroglycerin to promptly treat angina and the prior art teaches that both drugs treat angina.

Further, one would have been motivated to look to DE and utilize the instant amount of verapamil since the prior art teaches an amount of 5-25 mg is utilized in a sublingual/buccal

tablet. Additionally, a skilled artisan would have expected success in utilizing verapamil in GB's dosage form since GB teaches the only criticality of the medicament in the first layer is that it must be capable of being absorbed in the mouth and DE demonstrates verapamil satisfies this requirement; i.e. it is capable of being absorbed buccally or sublingually.

With regard to the recitation that the coating is applied as a film coating or as a compression coating, the examiner points out that application of the coating by compressing it around the core is a product by process limitation. Thus, regardless of the process in which the coating is applied, the product yielded is the same. However, the examiner relies on Fennel to teach various coating methods. Fennel teaches tablets may be coated in various ways including instantly claimed compression coating and tumble coating as taught by GB. Thus, a skilled artisan would have expected results by utilizing a coating compression rather than the method taught by GB since Fennel teaches both manners are conventionally known and utilized for coating cores.

Note that it is the examiner's position that the prior art's readily dissolvable outer layer will implicitly have the dissolving time of claim 48 since the immediate layer is structurally similar to the instantly claimed intraoral layer.

With regard to claim 46, the examiner cites US 6,228,396 wherein the references states that a coating such as shellac provides for a breakup in about 3-4 hours. See column 3, lines 9-25.

(C) Claims 41, 51, and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over GB 800,973 in view of Remington's Pharmaceutical Sciences, Eighteenth Edition (1990), page 844 optionally in further view of Fennel et al (3,898,323).

GB teaches a multi-layered tablet comprising 1) the outer coating contains a medicament that readily dissolves in the mouth 2) a signal layer containing a distinctive flavor between the outer coating and core and 3) an enteric layer around an oral medicament core to be swallowed. See figures and column 2 in its entirety. The outer coat is taught to readily dissolve in the mouth. See column 2, lines 59-65. GB discloses that the enteric layer may be manipulated with a certain thickness to release the medicament in a given area or time, which is known in the art. See page 2. GB discloses that the tablet provides a means for dosing a patient with at least two separate medicaments, one of which is to be absorbed in the mouth and the other in the gastro-intestinal tract. See column 2, lines 47-59. Note that "enteric coating" provides release in the intestine.

Example 1 teaches the immediate drug on the outside as N-isopropylarterenol (molecular weight 211.26) and the delayed core is theophyllin. Example 2 teaches an inner core comprising a drug and alginic acid (sustained release polymer) is coated with three coats of shellac and then an alarm layer is coated over this. The immediate layer comprising 10% nitroglycerin (molecular weight of 227.09) is dusted. The tablet is utilized to promptly treat angina followed by the delayed action of pentaerithrytol in the inner core. Optionally the outer medicament layer may comprise the flavor components of the alarm layer.

Although GB teaches using nitroglycerin in an amount of 10% for the outer coating, GB does not teach the nitroglycerin dosage in instant terms, i.e. instant 0.001mg to 50mg.

Remington's Pharmaceutical Sciences discloses that nitroglycerin has a molecular weight of 227.09 and that dose nitroglycerin is used. The reference teaches for buccal tablets 1mg is used and for sublingual tablets for an acute attack 0.15-0.6mg is used. See page 844.

Fennel teaches the process of a coating a core by tumbling the core in a drum containing the coating material or spray coating. Fennel teaches alternatively the coating may be applied over the tablet core by compressing the core with a tablet press. See column 3, lines 14-30.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to look to the teachings Remington's Pharmaceutical Sciences and utilize the instant amount of nitroglycerin. One would have been motivated to do so since Remington's teaches the instant concentration of nitroglycerin that is routinely used to treat angina. Further, Remington teaches the use of 0.15-0.6 mg for an acute attack and GB teaches the use of the outer layer of nitroglycerin for prompt relief of angina. Lastly, it should be noted that generally difference in concentrations do not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such as concentration is critical. See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

The recitation that the coating is applied as a film coating or as a compression coating is a product by process limitation and regardless of the process in which the coating is applied, the product would be the same. However, the examiner relies on Fennel to teach various coating methods. Fennel teaches tablets may be coated in various ways including instantly claimed compression coating and tumble coating as taught by GB. Thus, a skilled artisan would have expected results by utilizing a coating compression rather than the method taught by GB since Fennel teaches both manners are conventionally known and utilized.

(D) Claims 33-36, 38-40, 42-44, 47-48, 52-53, 55-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/35296 to Johnson.

Johnson teaches a composition and method of making a chewing gum wherein an active agent is contained in the gum core and in the coating. The active in the coating agent may be further mixed with a flavor. See abstract. Johnson teaches the medicament in the coating provides a quick release of the active into the saliva. After chewing the gum, the pressure within the buccal cavity forces the active into the systemic system. See page 4. Johnson teaches the gum coating containing a medicament will have a fast release whereas the core containing a medicament may be encapsulated for a slow release. See page 15. Johnson teaches a chewing time proving slow release for 40 minutes. See page 8.

Johnson teaches a variety of medicament including the instantly claimed buspirone disclosed as an antidepressant and verapamil disclosed as a cardiovascular drug. See page 11-12. The medicaments are provided in an amount of 12 micrograms to 250 milligrams. See page 13.

The chewing gum portion contains a gum base and flavoring agent. See page 17. The gum coating contains flavoring agents, cellulose polymers, antitack agents (glidants), colorants, plasticizers, etc.. See page 22-23 and page 24 (last paragraph).

Johnson does not exemplify the instantly claimed active agents.

However, it would have been obvious for one of ordinary skill in the art at the time the invention was made to utilize the instant drugs buspirone or verapamil. One would have been motivated to utilize the buspirone or verapamil with the expectation of similar results since Johnson suggests this. Further, the selection of a particular drug is dependent on the desired treatment. Thus, for instance, if a skilled artisan desired treat angina, one would have been motivated to utilize a cardiovascular drug such as verapamil.

With regard to claims 35-36, note that the definition of a tablet is a small pellet to be taken orally; thus Johnson reads on this limitation. Also on page 17, Johnson teaches "tableting" the chewing gum. The definition of a capsule is a small soluble container enclosing an oral medication.

Note that it is the examiner's position that the prior art's readily dissolvable outer layer will implicitly have the dissolving time of claim 48 since the immediate layer is structurally similar to the instantly claimed intraoral layer.

(E) Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/35296 to Johnson in view of Jao et al (5,310,561).

The teachings of Johnson have been set forth above. Johnson teaches a variety of medicaments depending on the desired treatment.

Johnson does not teach the use of ondansetron (325 Daltons).

Jao teaches the administering ondansetron in an amount of 1mg to 400mg to the buccal mucosa for the treatment of nausea. See claim 4.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to utilize ondansetron in Johnson's gum coating. One would have been motivated to do so if one wanted to treat nausea. Further, one would have expected success since Johnson teaches the gum coating contains an active that administers the drug to the buccal mucosa.

(F) Claims 33-36, 38-39, 43-44, 47-49, 52-53, and 55-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neuser et al (PGPUB 2001/0002999) in view Lewis et al (4,661,492) in further view of Liedtke (5,686,122).

Neuser teaches an analgesic combination wherein the core of the tablet contains a systemically acting analgesic and the outer coating contains a locally acting analgesic/anaesthetic. The locally acting analgesic has a rapid onset and the systemic portion has a sustained action for a duration of at least 3 hours. See claim 1 and paragraph 0015. The local analgesic is a drug that has an onset action of one minute and particularly 30 seconds and is utilized in an amount of 2-30mg. See paragraph 0007. The local analgesic is selected from lidocaine (234.34), prilocaine (256.77), mepivacaine, procaine (272.77), etc., with a preference for benzocaine (165.19). See paragraph 0009 and 0014. Neuser teaches preparing the formula by press coating (compression coating). Neuser teaches a core comprising naproxen, microcrystalline cellulose, and orange flavor is coated with a coating syrup comprising lidocaine. See examples.

Neuser does not teach the instant drugs claimed.

Lewis et al teach an analgesic composition that may be in the form of a sublingual or parenteral form. The analgesic, buprenorphine, is included in the therapeutic amount of 0.1 mg to 0.4mg sublingually for the treatment of pain. See column 2, lines 61-66.

Liedtke teaches local anaesthetics including buprenorphine, lidocaine, prilocaine, and mepivacaine. See column 3, lines 1-10.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Neuser et al and Lewis et al and substitute Neuser's anaesthetics with the instantly claimed drug buprenorphine in the instant amount. One would have been motivated to do so since Lewis et al teach the analgesic effects of buprenorphine in a sublingual tablet form. Further, Liedtke teaches the anaesthetics taught by Neuser et al and

instant buprenorphine function as local anesthetics. Thus, a skilled artisan would have expected similar results and success by substituting the prior art's anaesthetic with buprenorphine since the prior art establishes the functional equivalency.

With regard to claim 47, it is the examiner's position that the recitation "wherein the second oral portion is chewable and comprises at least one pharmaceutically acceptable excipient suitable for chewable medication" is intended use. Further, if the prior art structure is capable of performing the said intended use, then it meets the intended use. In the instant case, Neuser's GI portion is capable of being chewed and the excipients used in the core are also capable of being chewed, thus it meets the claim limitation.

(G) Claims 33-43 and 49-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barclay et al (5,053,032) in view of Panther et al (6,200,604).

Barclay et al disclose an osmotic device for delivering a beneficial agent. Barclay's tablet houses two regions, one for delivering a predetermined dosage via buccal administration of a drug and a second region for delivering the remainder of the dose to the GI tract (Note abstract, col. 8, lines 28-51). Further, the tablet contains a signaling in the form of a flavoring agent or coloring agent that alerts the patient that the buccal administration dosage has been delivered and the remainder may be swallowed (col. 3, lines 57-68, col. 5, lines 25-55). In a preferred embodiment the first active agent has a first flavor and the hydrophilic polymer layer containing the second portion contains a second flavoring agent. See column 5, lines 25-55. The reference discloses several drugs including instant drug prochlorperazine, nitroglycerine (227.09), ibuprofen (206.28), naproxen (230.26), levodopa (197.19), etc. that are suitable for the delivery device on column 10, line 50 to column 11, line 35. The drug is used in an amount of 0.05ng to

500 mg. See column 12, lines 23. Barclay discloses the process of making the device and compression of the layers (example 1). Osmagents such as sodium carbonate are taught in the osmotic device. See column 12 lines 27-45 and example 3. The device delivers the active agent over an extended period of time, i.e. 0.5-12 hours. See column 15, lines 15-20.

Example 3 discloses an oral osmotic device wherein the inner core contains 20.5 ibuprofen, 66.5% polyox, 5% HPMC, 7.5% sodium carbonate, and 0.5% magnesium stearate. This core is coated with a layer containing 20% ibuprofen (206.28 molecular weight), and 80% HPMC (cellulose). The overcoat layer is completely removed within about 15 minutes to 30 minutes. Further, the device contains a color-coding signaling system.

Although, Barclay teaches the instant drug prochlorperazine of independent claim 33, Barclay does not exemplify it and its dosage amount.

Panther teaches a sublingual buccal effervescent which contains an orally administrable drug in combination with an effervescent to promote the absorption of the medicament in the oral cavity. See abstract. Panther teaches the use of the effervescent as a penetration enhancer to influence the permeability of the medicament across the oral mucosa. See column 2, lines 5-11. Panther also teaches the prior art use of effervescent agents in buccal administered dosage forms to mask the taste of the medicament. See column 1, lines 30-40. Lastly, Panther teaches the use of a variety of medicaments in the sublingual formula. Panther exemplifies the use of prochlorperazine in the amount of 5 mg. See example 2. Lastly, Panther teaches the use of a variety of medicaments including the ones disclosed in US patent 5,234,957. US '957 discloses of drugs such as ibuprofen.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Barclay et al and Panther and utilize the instant amount of prochlorperazine since Panther teaches the instant amount of the prochlorperazine is utilized to administer the drug in the mouth. Further, one would have been motivated to utilize an effervescent agent in the buccal region of Barclay's device since Panther teaches the use of effervescent agents as penetration enhancers in sublingual/buccal tablets, which facilitates the permeation of the drug across the oral mucosa. Therefore, a skilled artisan would have been motivated to add an effervescent agent to increase the penetration of the drug through the oral mucosa. Therefore, the instant invention is prima facie obvious.

With regard to claim 47, it is the examiner's position that the recitation "wherein the second oral portion is chewable and comprises at least one pharmaceutically acceptable excipient suitable for chewable medication" is intended use. Further, if the prior art structure is capable of performing the said intended use, then it meets the intended use. In the instant case, Barclay's GI portion is capable of being chewed and the excipients used in the core are also capable of being chewed, thus it meets the claim limitation.

(H) Claims 33-57 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of US 6863901 and 1-20 of 11/041474. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications contain similar subject matter.

(10) Response to Argument

(A) Claims 33-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Appellant argues that since the oral portion can be delayed or sustained release, and it is swallowed, release occurs through the stomach and the intestine. Appellant argues even if the formulation is chewed and swallowed in the mouth, release occur in the intestine.

The examiner respectfully points out that the instant claims are directed to a formulation "wherein the second potion is either a sustained release or chewable formulation." Thus, the claims are not directed to a sustained release chewable formulation as argued by applicant. Therefore, if the second oral portion is chewed, then it is unclear how it is released in the intestine since the mastication process would cause the composition and the active to release in the mouth and not in the intestine. It is respectfully submitted that regardless of the formulation of the second portion, i.e. even if arguendo the second portion was formulated into a sustained release chewable formulation, the mastication process would break the integrity of the composition; thus releasing majority of the active in the mouth and not the intestine as required by the claim. It is noted that the appellant has not addressed this and merely repeats that it is released in the intestine.

Appellant argues that the claims will be amended to "a core" to remove the examiner's rejection and is solely done to further prosecution. However, appellant argues that the limitation is clearly supported if one looks at the "base claim".

The examiner acknowledges appellant's statement and points out that claims 33, 41, and 55 in which the lack of antecedent basis are independent claims. Thus, one cannot "look at the correct base claim" to understand the limitation since claims 33, 41, and 55 are the base claims. Further, the instant rejection is not directed to lack of support, the rejection is directed to indefiniteness; thus appellant's argument that one can look at the base claim for support is unclear.

Appellant argues that claim 37 defines the composition of claim 33, which is a multi-layer tablet wherein "the oral component comprises one or more inner layer of the tablet and the intraoral component comprises one or more outer layer of the tablet".

Firstly, it is noted that appellant has omitted the phrase "the" when discussing the limitation of claim 37. The word "the" causes the lack of antecedent basis in claim 37. The examiner respectfully points out that claim 37 is directed to "a multi-layer tablet wherein the second oral portion of the composition comprises one or more inner layers of the tablet and the first intraoral component comprises one or more of ***the*** outer layers of the multi-layer tablet." Therefore, "the outer layers" lacks antecedent basis and it is unclear what the outer layers refer to. Appellant has not addressed this and merely claims it is inherent in the claims itself.

(B) Claims 33-39, 41-50, and 51-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over GB 800,973 in view of Powell et al (6,140,319) in further view of DE 3338978 in further view of Fennel et al (3,898,323).

Appellant argues that GB '973 (Sterling) does not teach the first intraoral portion, which rapidly dissolves or disintegrates intraorally for buccal or sublingual absorption, comprising the instant active agent. Appellant argues that Sterling does not teach a second portion that is a

sustained or chewable formulation. Appellant argues Fennell only teaches a formulation containing miraculin and there is not disclosure of a second drug. Appellant argue that the mere fact that the references can be combined or modified does not render the resultant combination obvious. Appellant argues that Fennell is not concerned with a drug formulation wherein one portion is intraoral and the second is release for uptake in the stomach. Appellant argues that the examiner has not provided any motivation to combine the reference. Appellant argues that Fromming and Powell disclose compounds that may be incorporated into the claimed composition but do not teach one how to make the composition.

Firstly, the examiner points out that although independent claim 41 requires:

(a) a first portion that rapidly disintegrates in the oral cavity wherein the active has "a molecular weight not exceeding 350 Daltons **or** an active ingredient selected from the group consisting of Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil, Carfentanil, Nalbuphine, Droperidol, and Haloperidol" present in an amount between 1 micrograms and 50 mg , wherein the intraoral portion is a film coating applied to the core or a compression coating compressed around the core;

(b) a pharmaceutically acceptable effervescent agent which generates effervescence **or** a pharmaceutically acceptable signaling system, located between the first intraoral component and the second oral component, that is detectable by the patient upon substantial release of the pharmaceutically active ingredient in the first intraoral component when contacted with salivary fluid; and

(c) a second oral portion located within the first portion which contains a pharmaceutically active agent, which is released for uptake into the intestine in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved.

Sterling teaches a multi-layered tablet comprising (a) an outer coating that contains a medicament that readily dissolves in the mouth (b) a signal layer containing a distinctive flavor, (c) an enteric layer around an inner layer comprising an oral medicament, and (d) a core that can contains a medicament. See figure 1 and claim 1 in combination with claim 3.

Specifically example 2 teaches an inner core comprising pentaerithrytol tetranitrate which coated with three coats of shellac and then an alarm layer is coated over this. The immediate layer comprising 10% nitroglycerin (molecular weight of 227.09) is dusted. The tablet is utilized to promptly treat angina followed by the delayed action of pentaerithrytol in the inner core. Example 1 teaches outer layer comprising isopropylarterenol which has a molecular weight of 211.26.

Firstly, the examiner respectfully points out that nitroglycerin has a molecular weight of 227.09 and thus nitroglycerin is an active that is "less than 350 Daltons". Further, the examiner points out that page 10 of the instant specification clearly states that nitroglycerin is capable of being taken thorough the oral mucosa. Secondly, the examiner points out that shellac is a polymer used for enteric coating. Enteric is defined as: "Of, relating to, or being within the intestine." Enteric coatings are known in the art to delay release to the intestine. Further, appellant teaches shellac on page 28 as a suitable polymer for the enteric coating. Lastly, it is the examiner's position that the medicament core reads on chewable formulation since "chewable" is

an intended use recitation and does not impart any structure except that it must be capable of being chewed. In instant case, the core is capable of being chewed.

Sterling clearly teaches on column 1:

> This invention release to a multi-layered pill or tablet particularly adapted for medicinal use and having a medicinal core and an intervening taste-indicating layer or lamination, said lamination having an outer medicinal layer, which is soluble in the patient's mouth, to the end that the pill is held by the patient for absorption of the outer layer until the taste-indicating layer serving as an indication to the patient to swallow the tablet to contain the benefits of gastro-intestinal absorption of the medicament within the pill or tablet.

Therefore, Sterling by itself reads on independent claim 41.

With regard to independent claim 33 and 55, the examiner notes that Sterling does not teach the instant active agents and hence the examiner relies on the secondary references to cure this deficiency. Appellant argues that Sterling does not recognize that the medicament that dissolves in the outer layer must be capable of being absorbed in the mouth. The examiner respectfully disagrees. The mere fact that Sterling does explicitly state use appellant's terminology, i.e. "sublingual" or "buccal" or "intraoral", does not mean that Sterling does not implicitly teach this. This teaching is implicit in the fact that Sterling clearly teaches the "outer medicinal layer, "is soluble in the patient's mouth," and the inner core is swallowed for "benefits of gastro-intestinal absorption of the medicament within the pill or tablet." Note the above quoted paragraph. Sterling's disclosure that the outer layer dissolves in the mouth reads on "buccal" absorption. Sterling clearly differentiates between the inner core medicament, which "benefits [from] gastro-intestinal absorption" and the outer layer medicament is soluble in the mouth. Also note column 2, lines 47-55

> "The present invention provides a means for dosing a patient with at least two separate medicaments, one of which is to be absorbed in the mouth and the other in the gastro-intestinal tract".

Further, all of the examples utilize "prompt" acting medicaments in the outer layer. Both of the exemplified medicaments have a molecular weight of less than 350 Daltons. Thus, it is the examiner's position that Sterling implicitly teaches the outer layer medicament must be a drug capable of being absorbed in the mouth, i.e. buccal or sublingual absorption.

Therefore, the only teaching missing from Sterling is the instant drugs claimed in the Markush group. The examiner relies on the secondary reference to teach the functional equivalence of the instantly claimed verapamil and amlodipine with the prior art's nitroglycerin. Powell teaches amlodipine, verapamil, and nitroglycerin all function to treat angina (see column 4, lines 5-16) and the pharmaceutical forms includes buccal and sublingual forms (see column 3, lines 60-65). Moreover, Fromming teaches a verapamil in a buccal and sublingual tablet. Hence, meeting the requirement set forth by Sterling that the drug in the outer layer must be soluble in the mouth, i.e. capable of buccal administration. It is noted that appellant has not addressed the examiner's motivation and rather attacks the references individually. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Appellant argues the merits of the secondary references individually; however the examiner respectfully points out that the secondary references are only utilized to show that the obviousness of utilizing instant verapamil or amlodipine. Sterling teaches nitroglycerin to provide "prompt" relief of angina and the secondary references teach verapamil and amlodipine also promptly relieve angina. Again, the examiner points out that appellant clearly disclose

nitroglycerin as a suitable medicament for the first oral portion. Thus, the examiner motivation is that all three, verapamil, amlodipine, and nitroglycerin are known in the art as medicaments for promptly treating angina. Thus, the use of one over the other is obvious to those skill in the art since the art clearly establishes that verapamil, amlodipine, and nitroglycerin are functional equivalents.

With regard to appellant's argument that the molecular weight is critical to its uptake in the oral cavity, it is firstly pointed out that the features upon which applicant relies are not recited in the rejected claims 33-39, 42-50, 52-53, and 55-57. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore, applicant's purported inventive concept of only utilizing certain molecular weight drug is not even claimed. Moreover, the majority of the drugs claimed in independent claim 33 and 55 have a molecular weight over 350 Daltons.

With regard to Powell and Fennel not teaching the instant first intraoral portion and second oral portion and further teachings other active agents with a high molecular weight, the examiner points out that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In instant case, the primary reference, Sterling is not deficient in the teaching of a first intraoral potion and a second oral portion; Sterling clearly teaches this. The secondary references are only relied upon to cure

Sterling's deficiency of the lack of disclosure of the claimed drugs. The examiner's motivation is based on functional equivalency as discussed above.

Appellant argues that Sterling does not teach film coating or a compression coating.

The examiner respectfully submits this is a product-by-process limitation in independent claims 33 and 41. MPEP section 2113 states "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985). With regard to independent claim 55, the examiner has relies on Fennel to teach various coating methods. Fennel teaches that it is known in the art to coat tablets by tumbling the core, spray coating, or compressing the coat onto the core. A skilled artisan would have reasonably expected similar results by utilizing either methods to coat the tablets since Fennel teaches Sterling's method and the instant method are known and conventionally utilized for coating cores. Appellant's has not provided any unexpectedness of the instant process limitations.

Appellant argues that the prior art references teach a delayed release, the examiner respectfully points out that Sterling teaches a shellac coating (shellac is taught by appellant on page 28), which is an enteric coating over the core. An enteric coating delays release until the dosage form reaches the intestine. The definition of delayed release is "releasing a drug at a time later than that immediately following its administration". Thus, the release of the Sterling's core, once swallowed, is in fact delayed.

Appellant argues that the prior art references teach the first intraoral component disintegrating within 10 minutes. As discussed in the rejection, it is the examiner's position that the prior art's readily dissolvable outer layer will implicitly have the instant dissolving time since the immediate layer is structurally similar to the instantly claimed intraoral layer. The examiner notes the examples utilize a composition comprising a drug, opadry, aspartame, flavoring, and water. Sterling teaches the immediate release layer comprising the drug, gelatin, sucrose, talc (colorant), and sodium metabisulfite (antioxidant). Sterling's immediate release layer does not contain any excipient that sustains release, such as a cellulose polymer. Thus, the examiner has made a reasonable rationale showing that the prior art will have the instant dissolving time. Since the Patent Office is not capable of testing the properties of the product, the burden shifts to appellant to prove otherwise. However, appellant has not provided any evidence or arguments rebutting the examiner's position as required by MPEP 2112.

Appellant argues that none of the prior art references teach a sustained release. Firstly, the examiner points out that dependent claim 43 is broadly directed to a "sustained release" without any parameters. Thus, the term "sustained" is a relative term and any time frame can read on it without any parameters set forth. Further, the examiner points out that Sterling uses 2% alginic acid in the core. The examiner points out alginic acid is sustained release excipient as evidenced by US 20030228361, [0067]. The examiner notes that the examples in appellant's disclosure utilize the sustained release polymer in an amount of 2-8%. Thus, the examiner has made a reasonable rationale showing that the prior art will have the sustained release. Since the Patent Office is not capable of testing the properties of the product, the burden shifts to appellant

to prove otherwise. However, appellant has not provided any evidence or arguments rebutting the examiner's position as required by MPEP 2112.

Appellant argues that none of the prior art references teach the second portion with a chewable excipient. The examiner respectfully submits that if the prior art structure is capable of performing the said intended use, then it meets the intended use. In the instant case, Sterling's core comprises excipients that are capable of being chewed; thus meeting the claim limitation. Further, the examiner points out that page 25, lines 20-25 of the instant disclosure states, "pharmaceutically acceptable excipient for chewable tablets selected from the group consisting of lactose, sorbitol, mannitol, sugar, **starch**, citric acid, and **magnesium stearate**, optionally with a flavoring agent." The examiner points out that Sterling teaches starch and magnesium stearate in the core composition. Clearly the core is capable of being chewed and contains "chewable excipients".

Appellant argues that none of the references teach the claims range of 1 microgram to 50 milligram of the drugs. The examiner points out that Sterling teaches the amount of the drug in terms of weight percent and Fromming teaches the use of verapamil in the amount of 5-25mg in a sublingual or buccal tablet. See abstract.

(C) Claims 41, 51, and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over GB 800,973 in view of Remington's Pharmaceutical Sciences, Eighteenth Edition (1990), page 844 optionally in further view of Fennel et al (3,898,323).

Appellant argues that Sterling does not teach an effervescent agent or a signaling system located between the intraoral and oral component. Appellant argues that Sterling does not teach film coating or a compression coating.

As discussed extensively above, independent claim 41 requires a effervescent agent **or a signaling system.** Specifically example 2 teaches an inner core comprising pentaerithrytol tetranitrate which coated with three coats of shellac and then an alarm layer is coated over this. The immediate layer comprising 10% nitroglycerin (molecular weight of 227.09) is dusted. The tablet is utilized to promptly treat angina followed by the delayed action of pentaerithrytol in the inner core. Example 1 teaches outer layer comprising isopropylarterenol, which has a molecular weight of 211.26, an alarm layer, and a core comprising benzylephedrine, theophyllin, and phenobarbital. The isopropylarterenol layer is applied to the tablets by tumbling.

Clearly Sterling teaches a signaling layer. The fact that Sterling uses the term "alarm layer" and appellant uses the term "signaling layer" does not distinguish the instant invention over the prior art since both act to signal the patient that the tablet should be swallowed.

Appellant argues that the prior art does not teach an effervescent agent.

The examiner respectfully points out that claim 41 is directed to, "a pharmaceutically acceptable effervescent system which generates effervescence or a pharmaceutically acceptable signaling system."

Appellant argues that none of the prior art references disclose the general concept of a two component formulation for initial intraoral delivery followed by oral delivery; a rapidly disintegrating or dissolving coating over an intraoral drug, the selection of a drug for intraoral delivery in a dosage range of between 1 and 50 mg, nor the combination with a sustained release or chewable second component for oral delivery.

Sterling clearly teaches on column 1:

> This invention release to a multi-layered pill or tablet particularly adapted for medicinal use and having a medicinal core and an intervening taste-indicating layer or lamination, said lamination

> having an outer medicinal layer, which is soluble in the patient's mouth, to the end that the pill is held by the patient for absorption of the outer layer until the taste-indicating layer serving as an indication to the patient to swallow the tablet to contain the benefits of gastro-intestinal absorption of the medicament within the pill or tablet.

Although Sterling teaches 10% nitroglycerin in the outer layer to treat angina, Sterling does not teach the amount of nitroglycerin in grams. Thus, the examiner relies on Remington to cure Sterling's deficiency. The reference teaches for buccal tablets 1mg is used and for sublingual tablets for an acute angina attack 0.15-0.6mg. Thus, it is within the skill of an artisan to utilize the appropriate amount of nitroglycerin since Remington's teaches the conventional dosage amount.

With regard to the application of the coating, the examiner respectfully submits this is a product-by-process limitation. MPEP section 2113 states "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, If the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985). Moreover, the examiner has also relied on Fennel to teach various coating methods. Fennel teaches that it is known in the art to coat tablets by tumbling the core, spray coating, or compressing the coat onto the core. A skilled artisan would have reasonably expected similar results by utilizing either methods to coat the tablets since Fennel teaches Sterling's method and the instant method are known and conventionally utilized for coating cores. Appellant's has not provided any unexpectedness of the instant process limitations.

(D) Claims 33-36, 38-40, 42-44, 47-48, 52-53, 55-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/35296 to Johnson.

Appellant argues that Johnson does not teach an agent that is released and absorbed intraorally and an agent that is released and absorbed orally. Appellant argues that the claimed composition is designed to be swallowed once the intraoral layer is disintegrated. Appellant argues that chewing gums are not normally swallowed and thus Johnson does not teach swallowing a tablet or capsule.

Firstly, the examiner respectfully points out that independent claim 33 is directed to a "pharmaceutical composition" and the claims is not directed to a tablet or capsule as argued by appellant. Therefore, Johnson's chewing gum reads on appellant's "pharmaceutical composition." With regard to dependent claim 35 and independent claim 55, the examiner points out that the definition of a tablet is, "small flat pellet of medication to be taken orally". Further, on page 17, Johnson teaches "tableting" the chewing gum. Thus, it is respectfully submitted that Johnson's chewing gum reads on "tablet" since it is a small, flat dosage form that is administered orally.

Secondly, it is respectfully pointed out that appellant's arguments are directed to the intended use of the composition and the instant claims are directed to a product. Moreover, assuming arguendo that the intended use is given weight, the examiner points out that the claims do not require swallowing the second portion. The claims merely require that the second portion is "released for uptake in the intestine in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved, wherein the second portion is either a sustained release or chewable formulation. Cleary, the claims do not exclude the mastication process since appellant

claims a "chewable formulation" and the second portion is not limited to swallowing. The examiner respectfully points out that Johnson's core reads on instant "chewable formulation."

Further, the examiner respectfully points out that appellant has not fully addressed the examiner's 112, second paragraph rejection based on the fact that if the composition is chewed then it cannot be released in the intestine. This issue is pertinent to the instant rejection over Johnson since Johnson teaches a chewable core, but as argued by appellant, this core is not released in the intestine. It is unclear how appellant's core that is chewed is capable of release in the intestine, whereas (as argued by appellant) Johnson's chewable core is not. Appellant has not provide any structural limitations to differentiate over Johnson's chewable core. The only argument provided by appellant is that the core can be chewed and swallowed. The examiner respectfully submits that Johnson's core is also chewable and Johnson's gum is also capable of being swallowed. Appellant argues that chewing gums are not normally swallowed. It is noted that appellant argues that chewing gums are not normally swallowed and yet also claims a "chewable formulation". The examiner respectfully points out that this instant claims are directed to products and not the method of administering. Thus, the prior art need only be capable of the intended use. Further, as discussed above, the claims do not recite this intended use limitation of swallowing. The claims only require the second portion in a sustained release formulation or chewable formulation.

Appellant argues that none of the prior art references teach the second portion with a chewable excipient. The examiner respectfully submits that if the prior art structure is capable of performing the said intended use, then it meets the intended use. In the instant case, clearly Johnson teaches a chewable core. Further, the examiner points out that page 25, lines 20-25 of

the instant disclosure states, "pharmaceutically acceptable excipient for chewable tablets selected from the group consisting of lactose, **sorbitol**, **mannitol**, sugar, starch, citric acid, and magnesium stearate, optionally with a flavoring agent." The examiner points out that Johnson teaches sorbitol, mannitol, and flavors in the core composition. See Table 32 for instance. Clearly the core contains "chewable excipients".

Independent claim 33 is directed to a) a first portion that rapidly disintegrates comprising an active ingredient selected from the group consisting of Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil, Carfentanil, Nalbuphine, Droperidol, and Haloperidol" present in an amount between 1 micrograms and 50 mg, wherein the intraoral portion is a film coating applied to the core or a compression coating compressed around the core;

(b) a second oral portion located within the first portion which contains a pharmaceutically active agent, which is released for uptake into the intestine in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved, which is **either** a sustained release **or** chewable formulation.

Independent claim 55 is directed to a process of making a composition comprising the above components.

As discussed in the rejection, Johnson a composition and method of making a coated chewing gum comprising an active agent in the gum core and an active in the coating. On page 4, Johnson teaches:

> The medicament or active agent is present within the coating of a chewing gum composition. It has been found that by adding the active agent to a gum coating, the medicament or active agent is quickly released from the chewing gum into saliva. Possibly, saliva coats the oral tissues under the tongue (sublingual) and the sides of the mouth where the drug may partition from the saliva into the oral mucosa.

On page 15, Johnson teaches:

> Medicament actives may also be combined in a coated chewing gum product. A single active may be added to a gum coating for fast release and also added to the gum center with or without encapsulation for slow release. If the active has an affinity for the gum base, it may naturally give a slow release without encapsulation. If the active is fast release, it would have to be encapsulated or entrapped for the desired time release.

Thus, clearly Johnson teaches a sustained release "chewable" core comprising an active and a coating comprising an active for fast release. The only teaching lacking in Johnson is the exemplification of the instant drugs. However, page 11, line 25 teaches buspirone as a suitable active, verapamil on page 12, line 2, and amlodipine on page 12, line 3, to name a few. Johnson teaches the medicaments are provided in an amount of 12 micrograms to 250 milligrams on page 13. Therefore, it is the examiner's position that it is within the skill of an artisan to select a appropriate drug according to the disease or symptom to be treated. For instance, Johnson teaches verapamil is a cardiovascular agents; thus a skilled artisan would have been motivated to specifically select verapamil to treat angina.

Appellant argues that none of the prior art references teach a sustained release. Firstly, the examiner points out that dependent claim 43 is broadly directed to a "sustained release" without any parameters. Thus, the term "sustained" is a relative term and any time frame can read on the phrase without any parameters set forth. With regard to claim 44 which is directed to a release *over* 0.5-24 hours release, Johnson teaches on page 8 a slow release over 40 minutes.

(E) Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/35296 to Johnson in view of Jao et al (5,310,561).

Appellant argues that claim 57 depends on claim 55, which is directed to a composition comprising a tablet core and a at least one layer. Appellant argues that chewing gums are not tablets. Appellant argues Jao describes a dosage form that surrounds a lumen comprising the drug, a driving means, and an exit means. Appellant argues one cannot combine a chewing gum with the dosage forms taught by Jao.

As discussed above, the examiner points out that the definition of a tablet is, "small flat pellet of medication to be taken orally". On page 17, Johnson teaches "tableting" the chewing gum. Thus, it is respectfully submitted that Johnson's chewing gum reads on "tablet".

With regard to Jao, the examiner respectfully points out that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Claim 57 requires a drug having a molecular weight of less than 350 Daltons. In instant case, the examiner merely relies on Jao to teach the instant drug ondansetron (325 Daltons) and not the dosage form since Johnson is not deficient in this sense. Further, it is respectfully pointed out that regardless of the dosage form, the drug will retain its properties. Meaning, the effect of the drug will remain the same irrespective of ondansetron's formulation into an oral versus topical formulation.

Johnson teaches the gum may contain various active agents and treat various symptoms. Johnson on page 12:

> It is envisioned that depending on the active agent or medicament, the resultant chewing gum can be used to treat inter alia: coughs, colds, motion *sickness*; allergies; fevers; pain; inflammation; sore throats; cold sores; migraines; sinus problems; diarrhea; diabetes, gastritis; depression; anxiety, hypertension; angina and other maladies and symptoms.

Jao teaches ondansetron treats nausea. Thus, if one desired to treat nausea one would have been motivated to utilize ondansetron. Again, the fact that Jao teaches a different dosage form will not change ondansetron's function; ondansetron will treat nausea regardless of its formulation in a osmotic device or a chewing gum.

(F) Claims 33-36, 38-39, 43-44, 47-49, 52-53, and 55-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neuser et al (PGPUB 2001/0002999) in view Lewis et al (4,661,492) in further view of Liedtke (5,686,112).

Appellant argues that the claimed composition contains a first intraoral portion and a second oral active agent, wherein the second portion is either a sustained release or chewable formulation. Appellant argues that neither Lewis nor Liedtke cure Neuser's deficiencies. Appellant argues that a combination of Lewis and Neuser would result in a formulation having as a fast acting component buprenorphine and as a second component a systemically acting analgesic. Appellant argues Neuser teaches the local analgesic must have an rapid action with a short duration and buprenorphine is a long acting drug. Therefore, appellant argues there is not motivation to substitute Neuser's anesthetics with buprenophine as asserted by the examiner.

As acknowledged by appellant, Neuser teaches a core comprising a sustained release composition comprising a systemic analgesic and a coating comprising locally acting analgesic.

Further, as acknowledged by appellant the combination of references would provide a formulation having as a fast acting component buprenorphine and as a second component a systemically acting analgesic.

Appellant argues that Neuser teaches away from buprenorphine since buprenorphine is a longer acting local anesthetic. The examiner points out that Neuser only teaches that it is *preferable* that the local analgesic has an active time of 0.5-120 minutes. It is respectfully submitted that "Disclosed examples and preferred embodiments do not constitute a teaching away form the broader disclosure or nonpreferred embodiment". In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). The disclosure is not limited to analgesics with a action time of 0.5-120 minutes. This is implicit from the paragraph [0009] in which Neuser teaches various actives including mepivacaine and bupivacaine to name a few. Mepivacaine has a duration of 2-3 hours and bupivacaine has a duration of 3-5 hours. Thus, Neuser does not teach away from longer acting analgesics. The criteria set forth in Neuser is that the outer layer drug must be a local analgesic, which buprenorphine meets. Liedtke teaches buprenorphine, lidocaine, prilocaine, and mepivacaine are local anesthetics (analgesics).

As set forth in the rejection, Neuser is only lacking in the teachings of the instantly claimed drugs. Thus, the examiner relies on Lewis and Liedtke to cure this deficiency. Lewis 0.1-0.4mg teaches buprenorphine in a sublingual form in the amount of 0.1-0.4mg and Liedtke teaches the functional equivalence of Neuser's local analgesics and instant buprenorphine.

Appellant argues that Liedtke teaches a topical formulation and not an oral formulation.

It is respectfully pointed out that regardless of the dosage form, the drug will retain its properties. Meaning, the property of "acting as a local analgesic" will remain the same

irrespective of the local analgesic being formulated into an oral versus topical formulation. Clearly buprenorphine can be formulated into oral formulations as taught be Lewis.

Appellant argues that the prior art references do not teach sustained release or a sustained release over 0.5-24 hours.

The examiner points to paragraph [0013]:

> The local analgesics preferably employed as element A are rapidly acting and have an optimal duration of action lasting 0.5 to 120 minutes, preferably 2 to 60 minutes, in particular 5 to 30 minutes. The systemic analgesics preferably used as element B are those where a significant action has its onset after 15 minutes and lasts for up to 24 hours, preferably those whose action has its onset after 20 minutes and lasts for up to 12 hours, in particular up to 8 hours. Moreover example 1 discloses the core has a release over 3 hours.

Appellant argues that the prior art does not teach the first intraoral component disintegrating within 10 minutes (dependent claim 48). It is the examiner's position that the prior art's readily dissolvable outer layer will implicitly have the instant dissolving time since the immediate layer is structurally similar to the instantly claimed intraoral layer. The examiner notes the examples utilize a composition comprising a drug, opadry, aspartame, flavoring, and water. Neuser teaches the outer release layer comprising the drug and syrup. Neuser's outer layer does not contain any excipients that sustains release, such as a cellulose polymer. Thus, the examiner has made a reasonable rationale showing that the prior art will have the instant dissolving time. Since the Patent Office is not capable of testing the properties of the product, the burden shifts to appellant. However, appellant has not provided any evidence or arguments rebutting the examiner's position as required by MPEP 2112.

Appellant argues that none of the prior art references teach the second portion with a chewable excipient. The examiner respectfully submits that if the prior art structure is capable of performing the said intended use, then it meets the intended use. In the instant case, Sterling's

core comprises excipients that are capable of being chewed; thus meeting the claim limitation. Further, the examiner points out that page 25, lines 20-25 of the instant disclosure states, "pharmaceutically acceptable excipient for chewable tablets selected from the group consisting of lactose, sorbitol, mannitol, **sugar**, starch, citric acid, and magnesium stearate, optionally with a flavoring agent." The examiner points out that Neuser teaches sucrose (sugar) in the core composition. see example 1. Clearly the core is capable of being chewed and contains "chewable excipients".

(G) Claims 33-43 and 49-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barclay et al (5,053,032) in view of Panther et al (6,200,604).

Appellant argues that Barclay teaches an osmotic device. Appellant argues the device comprises a wall surrounding a compartment housing, a layer of an agent insoluble to very soluble in aqueous biological fluids such as saliva and a layer of fluid swellable hydrophilic polymer. It is argued that the device contains a passageway in the wall connects the agent with the exterior of the device and the agent is released from the device by the combined actions of fluid being imbibed therein. Appellant argues that the overcoat layer is completely removed in 15-30 minutes. Appellant argues that the instant invention is directed to a device that immediately release within 10 minutes. Appellant argues that the second portion degrades from a sustained release matrix and it is not release by "being pushed out" as described by Barclay. Appellant argues that this teaches away from the instant invention since the invention requires the intraoral portion is rapidly released.

Barclay teaches on page 8, lines 28-51:

> [T]he device of the present invention can be used to extend the absorption period of a drug which might be poorly absorbed throughout certain portions of the GI tract, such as the colon. In such a

> case, it may be desirable **to administer a predetermined percentage of a dose of the drug buccally followed by delivery of the remaining dose of drug in the device within the GI tract.** One example of such a drug is captopril, an anti-hypertensive used for the treatment of heart disease. Another example is the drug cimetidine, a histamine H.sub.2 receptor antagonist used for the treatment of duodenal and gastric ulcers. In such cases, the device 10 may be provided with a mark or line 19 on the external surface of wall 12 (See FIG. 2). The position of the line 19 corresponds to the delivery of the predetermined percentage of the dose from the device 10. Thus, when the interface 18 between the hydrophilic polymer layer 16 and drug 14 layers becomes aligned with the exterior line 19 on wall 12, the patient is alerted to the fact that the predetermined percentage of the dose of drug has been delivered. At this point, the patient simply swallows the device and the remaining portion of drug in device 10 is administered through the GI tract.

Therefore, clearly Barclay teaches a portion that administers a drug buccally and a second portion that administers the drug to the GI tract.

Independent claim 33 and 55 require a drug selected from Buprenorphine, Parecoxib, Aceclofenac, Buspirone, Ipsapirone, Fexofenadine, Loratadine, Dexbrompheniramine, Temelastine, Verapamil, Amlodipine, Ergotamine Tartrate, Dihydroergotamine, Ondansetron, Prochlorperazine, Sildenafil, Alprostadil, Sufentanil, Lofentanil, Carfentanil, Nalbuphine, Droperidol, and Haloperidol. Independent claim 41 id directed to the above drugs ***or*** a drug with a molecular weight not exceeding 350 Daltons.

Barclay teaches several drugs including instant prochlorperazine claimed in independent claims 33 and 55 and drugs with a molecular weight of less than 350 Daltons claimed in independent claim 41 such as nitroglycerine (227.09), ibuprofen (206.28), naproxen (230.26), levodopa (197.19). Thus, the only teaching missing in Barclay is the exemplification and dosage amount of the instant drug prochlorperazine. The examiner relies on Panther to teach the dosage amount of prochlorperazine in a sublingual (buccal uptake) dosage form.

With regard to appellant's argument that Barclay teaches an osmotic device, the examiner respectfully points out that the instant claims recite "comprising" claim language; thus the claims

do not exclude Barclay's passageway. Appellant has repeatedly argued that the instant invention is not an osmotic device; however appellant has not provided any structural limitations to structurally distinguish the instant invention from a osmotic release device. The claims do not recite a sustained release *matrix* in which the drug disintegrates from, as argued by appellant. Again the examiner points out that the claims are directed to the a) a first portion that rapidly disintegrates comprising (b) a second oral portion located within the first portion which contains a pharmaceutically active agent, which is released for uptake into the intestine in a therapeutically effective amount after the intraoral portion has disintegrated or dissolved, which is **either** a sustained release **or** chewable formulation. Clearly the claims are not limited to a sustained release matrix.

Secondly, the examiner points out that the independent claims are not directed to the first portion dissolving in 10 minutes as argued by appellant. Dependent claim 48, which is directed to a dissolving time of 10 minutes, is not rejected under Barclay. Thus, appellant's argument with regard to claim 48 is moot. With regard to appellant's argument that since Barclay teaches a dissolving time of 15-30 minutes and is not considered rapid, the examiner respectfully submits that "rapidly dissolves or disintegrates" is a relative term without any parameters. The instant specification does not explicitly define "rapid release" as a dissolving time of 10 minutes or less. Clearly the independent claims are not limited to a dissolving time of 10 minutes or less, hence this limitation is claimed in a dependent claim. Thus, the broadest most reasonable interpretation is applied. Barclay teaches in example 3, "the ibuprofen containing overcoat provides a loading dose which is quickly delivered to the patient upon retention in the mouth. Generally, the overcoat layer will be completely removed by patient sucking within about 15 to about 30

minutes. This is especially useful in cases where there is an initial delayer between the time when the device is place in the mouth of the patent and the time when the device benefits pumping the drug." Thus, the overcoat has a rapid release compared to the core. Note that this example also reads on the dependent claims requiring "delayed release".

Appellant argues that Barclay teaches an osmotic device and thus one would not be motivated to chew an osmotic device. The examiner points out that the recitation of "chewable formulation" does not limit the claim since the term chewable is intended use and does not impart a structural limitation. Therefore, the patentability lies with the product/composition and not the use of the product after administration. Thus, regardless if one would have been motivated to chew the Barclay's core or not, it is clearly capable of being chewed and thus meets the intended use limitation.

Appellant argues that Barclay teaches away from a sustained release portion. This argument is perplexing since clearly Barclay teaches about 5% hydroxypropylmethylcellulose (HPMC) in the core of the device (see examples) and this polymer is recognized in the art to impart a sustained release. The examiner points to page 25, line 2 of the instant specification which teaches HPMC as the sustained release polymer. The instant examples utilize 2-8% of the sustained release polymer to provide a "sustained release" and Barclay utilizes 5% in example 3.

(H) Claims 33-57 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of US 6863901 and 1-20 of 11/041474. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications contain similar subject matter.

Appellant states that a Terminal Disclaimer will be filed to overcome the double patenting rejection upon indication of allowance.

The examiner acknowledges appellant's wiliness to file a Terminal Disclaimer.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Sharmila S. Gollamudi

Conferees:

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VERAPAMIL AND GALLOPAMIL AND THEIR PHYSIOLOGICALLY TOLERATED SALTS FOR RESORPTIVE APPLICATION ON THE ORAL MUCOSA, NASOPHARYNGEAL CAVITY, AND THE RECTUM

[Verapamil und Gallopamil und ihre physiologisch vertraeglichen Salze zur resorptiven Anwendung auf den Schleimhaeuten des Mundes, des Nasen-Rachen-Raums und des Rektums]

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VERAPAMIL AND GALLOPAMIL AND THEIR PHYSIOLOGICALLY TOLERATED SALTS FOR RESORPTIVE APPLICATION ON THE ORAL MUCOSA, NASOPHARYNGEAL CAVITY, AND THE RECTUM

Verapamil and gallopamil and their physiologically tolerated salts for resorptive application on the oral mucosa, nasopharyngeal cavity, and the rectum as cardiovascular therapeutic, as well as corresponding pharmaceutical preparations. The advantages of the intravenous administration with respect to the peroral administration are obtained with greater ease therewith. /2

Patent Claims

1. A tablet for sublingual or buccal ingestion as cardiovascular therapeutic containing as active ingredient, aside from the commonly used additives, 5 to 25 mg of verapamil or 3 to 15 mg of gallopamil, or respectively the same quantity of their physiologically tolerated acid addition salts.
2. A bitable or chewable capsule for resorption via the mucosa as cardiovascular therapeutic containing as active ingredient, aside from the commonly used additives, 5 to 25

[1] Numbers in the margin indicate pagination in the foreign text.

mg of verapamil or 3 to 15 mg of gallopamil, or respectively the equivalent quantity of one of their physiologically tolerated acid addition salts.

3. An oral spray for resorption via the oral mucosa as cardiovascular therapeutic containing as active ingredient, aside from the commonly used additives, verapamil or gallopamil or one of their physiologically tolerated acid addition salts.

4. A nasal spray for resorption via the oral mucosa as cardiovascular therapeutic containing as active ingredient, aside from the commonly used additives, verapamil or gallopamil or one of their physiologically tolerated acid addition salts.

5. A suppository for rectal application as cardiovascular therapeutic containing as active ingredient, aside from the commonly used additives, verapamil or gallopamil or one of

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their physiologically tolerated acid addition salts.

6. A rectal capsule for application as cardiovascular therapeutic containing as active ingredient, aside from the commonly used additives, verapamil or gallopamil or one of their physiologically tolerated acid addition salts.

7. A microclysma for rectal application as cardiovascular therapeutic containing as active ingredient, aside from the commonly used additives, verapamil or gallopamil or one of their physiologically tolerated acid addition salts dissolved in water or a physiologically tolerated oil.

8. An osmotic pump for rectal application as cardiovascular therapeutic containing as active ingredient, aside from the commonly used additives, verapamil or gallopamil or one of their physiologically tolerated acid addition salts.

9. A sniffable powder for resorption via the oral mucosa as cardiovascular therapeutic containing as active ingredient, aside from the commonly used additives, verapamil or gallopamil or one of their physiologically tolerated acid addition salts.

10. A use of verapamil or gallopamil and their physiologically tolerated salts for resorptive application as cardiovascular therapeutic on the oral mucosa, nasopharyngeal cavity, and the rectum. /4

VERAPAMIL AND GALLOPAMIL AND THEIR PHYSIOLOGICALLY TOLERATED SALTS FOR RESORPTIVE APPLICATION ON THE ORAL MUCESS, NASOPHARYNGEAL CAVITY, AND THE RECTUM

One of the better known and most effective cardiovascular therapeutics, in particular coronary dilators, is 3-aza-7-cyano-1,7-bis-(3',4'-dimethoxy phenyl)-3,8-dimethyl nonan (verapamil, in the following abbreviated as V.). Gallopamil (G.) is known to be structurally related to it and similar in its effect, but more effective by a factor of 2.5. Under "V." and "G." should be understood not only bases, but also physiologically tolerated acid addition salts. They are applied intravenously or perorally. Both application forms have disadvantages: the peroral application requires several times the intravenous dose, because the active ingredient reaches the liver when it is administered via the gastrointestinal tract and is partially decomposed therein before it can unfold its effect at the intended location (in particular the heart). In some patients, the metabolic decomposition in the liver is so intense, that the intended effect can only be achieved with high doses. If the liver is bypassed (for example, in the intravenous administration), not only a considerably smaller dose is required in order to achieve the same effect, but also the

required verapamil level in the blood serum is lower than in the peroral application.

However, the intravenous application requires, as a rule, a physician and is therefore more costly. /5

It was therefore an object of the invention to solve this dilemma, that is, to develop forms of application of V. and G. that preclude the mentioned disadvantages.

In such cases suggests itself the sublingual or buccal application, but the prerequisites for its success are frequently not fulfilled, namely a sufficient solubility in water to ensure their dissolution in saliva, on the one hand, and a sufficient solubility in fat to ensure a fast resorption by the oral mucosa, on the other hand. Because of their molecular structure, it must have appeared doubtful that V. and G. fulfilled these requirements.

Something similar applies for the application of bitable or chewable capsules, oral and nasal sprays, and sniffable powders, as well as for rectal and transdermal application.

Even though the buccal absorption of V. has already been analyzed with respect to its dependency from the pH value and in view of other variables, which are uninteresting for the practice (B. J. Davis and A. Johnson, Proceedings of the B.P.S.,

1979, page 434 P), the research does not show any evidence that V. is suitable for the practical buccal application; on the contrary, the findings that the resorption is highest at pH 10 and lowest at pH 5 rather discourages from a practical testing, because the pH of saliva is within the range of 5.8 to 7.1 (see Documenta Geigy, Scientific Tables, 7th Edition, 1968, Geigy Pharmzeutica Publishers, Wehr, Baden, page 639), that is, within the range in which the resorption is low according to this research. /6

It was discovered now that V. and G. are not only suitable for the mentioned and further new resorptive applications, but that they are even excellently suitable: the effect per mg increases by many times (2 to 8 times) with respect to the peroral application, and the patients in which the peroral administration was insufficient show a full response. Above all, the effect is faster.

The application of V. and G. on the oral mucosa, the nasopharyngeal cavity, and the rectum as cardiovascular therapeutic, as well as the agents or preparations for this purpose are therefore an object of the invention.

It is known that V. and G. are cardiovascular agents that have a broad above all antianginal and antihypertensive effect. They

act as calcium antagonists. As such, they reduce the tone of the smooth vascular musculature and therewith the aortal and left ventricular pressure and in the end the myocardial oxygen consumption. In addition, they have pronounced antiarrhythmic properties. An enumeration of all their known effects on the cardiovascular system would be too extensive. These effects are known to persons skilled in the art. They are all included under the term "cardiovascular therapeutic."

While the commercially available V. tablets for peroral ingestion contain 40 to 80 mg of V., only 5 to 25, preferably 15 to 20 mg of V. or 3 to 15, preferably 5 to 12 mg of G. (as free base or salt, respectively) are required according to the invention for the tablets for sublingual or buccal application as well as for the bitable and chewable capsules because of the bioavailability, which is many times higher. The mean latency time until the appearance of the substance in the blood serum /7 amounts to less than 1 minute in the sublingual or buccal application, and to 18 minutes in the peroral application. The method mentioned first is also much better suited than the peroral method for a fast arresting of acute cases of, for example, angina pectoris or acute arrhythmias. The effect is also more reliable, and the range of all the important

pharmacokinetic parameters is much lower than in the peroral application.

Also the nasal and the rectal application produce a fast resorption and prevent the disadvantages of the peroral application.

As commonly used physiologically tolerated organic or inorganic acids, of which are generally used their salts V. and G., are taken into consideration, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, or sulfuric acid, and as organic acids are considered, for example, oxalic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, malic acid, citric acid, salicylic acid, adipic acid, or benzoic acid. Others can be found in Advances of Medical Research, Volume 10, pages 224 to 225, Birkhaeuser Publishers, Basel and Stuttgart, 1966, or in the Journal of Pharmaceutical Sciences, Volume 66, 1977, pages 1 to 5.

The acid addition salts are obtained, as a rule, in a known manner by mixing the free base or its solutions with the corresponding acid or its solutions in an organic solvent, for example, a low alcohol, such as methanol, ethanol or propanol, or a low ketone, such as acetone, methyl ethyl ketone, or methyl isobutyl ketone, or an ether, such as diethyl ether, tetrahydrofurane or dioxan. For a better crystal deposition can

also be utilized mixtures of the mentioned solvents. Free bases are also used in some cases.

The composition of the sublingual or buccal tablets, bitable or chewable capsules, oral and nasal sprays, suppositories, rectal capsules, osmotic pumps, and sniffable powders according to the invention is the usual (aside from the active ingredient) and does not require a detailed description herein. Reference is made to the enclosed teachings and manuals, for example, Hagers Manual of Pharmaceutical Practice, 4th Edition, Springer Publishers, Berlin - Heidelberg - New York, 1967 to 1980, Volume VII A, or H. Sucker, P. Fuchs, and P. Speiser, Pharmaceutical Technology, Georg Thieme Publishers, Stuttgart, 1978.

The sublingual and buccal tablets are generally small, flat, compressed tablets, which dissolve faster under the tongue or less fast in the cheek pouches, and which are resorbed via the oral mucosa.

In order to produce the sublingual tablets according to the invention, 3 to 15 mg of gallopamil or 5 to 25 mg of verapamil, respectively as a base or as one of its salts, or a multiple thereof with 20 to 60 mg of lactose, glucose, sugar cane, mannitol, or another well dissolvable additive or mixtures of the mentioned substances are mixed and processed to a granulate

with one of the commonly used granulation methods using a commonly used granulation liquid, such as ethanol/water (for example, 60:40). An addition of buffers for the purpose of adjusting a specific pH value and flavor additives can take place. An addition of 0.5 to 3% of a water-soluble flowability control agent, for example, polyethylene glycol having a molecular weight of 4000, to the granulation liquid may be required in order to regulate the flowability. /9

After drying to the desired residual moisture occurs the compression to tablets having the usual properties of sublingual tablets in a suitable tablet-making machine. The production of the tablets can also occur via direct compression without previous granulation.

Bitable capsules (chewable capsules) in the sense of the invention are especially prepared soft gelatin capsules, which after being bitten release the contained V. or G. for resorption via the oral mucosa.

In order to produce bitable capsules (chewable capsules) are processed according to the known method 3 to 15 mg of gallopamil or 5 to 25 mg of verapamil, as base or as one of its salts, respectively, or a multiple thereof, 0.2 to 0.5 ml (or a multiple) of a suitable (physiologically tolerated, highly

viscous, and hydrophilic) oil, or another substances commonly used for this purpose (generally polyethylene oxide), in such a way that a compound with a good flowability is produced, in which the active ingredient is finely distributed (dispersed and diluted). Filling into soft gelatin capsules of a suitable size occurs preferably in a known manner by means of the Scherer method.

The suppositories according to the invention are V. or G. preparations having a form that is suitable for their insertion into the rectum, which soften, liquefy, or degrade in the rectum.

In order to produce the suppositories, 10 to 30, preferably 15 to 25 mg of gallopamil or 20 to 80, preferably 40 to 60 mg of verapamil, as a base or as one of its salts, respectively, or a multiple thereof are processed with the required quantity of suppository basic compound according to one of the usual methods

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in such a way that the active ingredient is finely distributed in the suppository compound. The mixture is poured in a known manner into a suppository mold. As basic compound are taken into consideration the commonly used substrates, such as hard fat. The weight of one suppository amounts as a rule to about 2 g.

The rectal capsules in the sense of the invention are pharmaceutical preparations that consist of a sheath of gelatin that dissolves and degrades under the physiological conditions of the rectum and release the V. or G. for resorption in the rectum. In order to produce rectal capsules, the active ingredients are processed according to the known method in the same quantity as for the suppositories with 0.4 to 1.0 ml (or a multiple thereof) of a suitable liquid, for example, a fatty oil, in such a way that a compound with a good flowability is produced, in which the active ingredient is finely distributed. The addition of an auxiliary substance that increases the consistency, for example, hardened oil or wax, as well as a surface active auxiliary substance in order to improve the wettability may be practical. Filling into soft gelatin capsules of suitable size occurs advantageously in the known way by means of the Scherer method.

Microclysmas in the sense of the invention contain a few ml of an aqueous or oily V. or G. solution for rectal application in an elastic plastic container having an attached cannula. In order to produce the microclysmas pursuant to the invention are again dissolved in the usual way the same active ingredient quantities as for suppositories and rectal capsules in 2 to 5 ml (or a multiple thereof) of water or a suitable vegetable oil.

To the aqueous solution can be added a viscosity increasing auxiliary substance, for example, sodium carboxy methyl cellulose (for example, 0.5%) in the concentrations that are usual therefor. The solution is filled into a rectiol of suitable size. /11

An oral spray in the sense of the invention is a mechanically sprayable solution on an aqueous basis, which contains 1 to 3 percent by weight of G. or 1 to 6 percent by weight of V., tastes better due to the addition of flavor additives, and has the capacity of adhering to the oral mucosa. The adhesion capacity is improved by means of viscosity increasing additives that reduce the surface tension, for example, by means of methyl cellulose and/or polyethylene glycol sorbitan monolaurate. The solution can contain water soluble, physiologically tolerated organic solvents in order to improve the solubility of the active ingredients. If required, the addition of a preservative may be practical, for example, p-hydroxy benzoic acid ester and sorbic acid and their salts.

Each nasal spray must be adhering, isotonic, and buffered within the physiological range. The nasal spray pursuant to the invention consists of an aqueous solution of V. or G. in the same concentrations as in the oral spray. The adhesiveness is

also achieved by means of the same additives. For the isotonization serves a mixture of the buffer salt and sodium chloride. As buffer salt is used, for example, sodium dihydrogen phosphate. The nasal spray also contains suitably a preservative, for example, benzalconium chloride.
A sniffing powder consists of a physiologically tolerated, water soluble solid substance as carrier for the active ingredient, which does not irritate the mucosa. The usual carrier is lactose. Also an aromatic substance can be added, for example, peppermint oil. In the case of the invention, the active ingredient concentration amounts to 0.2 to 3 percent by weight of G. or 0.2 to 6 percent by weight of V. /12

The active ingredient content of the osmotic pump pursuant to the invention (sheath of water insoluble material in a shape suitable for insertion into the rectum, which is filled with the active ingredient or its solution or dispersion, and has an ultrafine opening, through which the body fluid penetrates and the active ingredient can escape uniformly over a long period of time) contains the same quantities of V. or G. as the suppositories pursuant to the invention.

Example 1

Sublingual or Buccal Tablet

20 mg of verapamil hydrochloride are intensively mixed by wet granulation with 70 mg (or a respective multiple thereof) of previously ground celutabs in the usual way and then wetted with a 1:1 ethanol-water mixture. The compound is granulated through a filter with 0.8 mm mesh width. The granulate is dried and carefully sifted. In addition, a solution prepared with relatively little ether of 8.8 mg of cetyl alcohol or a multiple thereof is sprayed by fractions onto the granulate while stirring. If required, if there is a stronger agglomerate formation, it is again carefully sifted after the ether evaporates. In addition, 1.2 mg of aerosil or a multiple thereof are mixed in. The compression takes place by means of a tablet-making machine utilized for the production of pharmaceutical tablets with a press capacity of 12 to 18 kn.

Example 2

Sublingual or Buccal Tablet by Means of Direct Compression

8 mg of gallopamil hydrochloride, 70 mg of ground celutab, and 1.2 mg of aerosil (or a multiple thereof) are homogeneously mixed in a suitable mixer. In addition, the etheric solution of

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cetyl alcohol mentioned in Example 1 is mixed in by fractions. The produced mixture is dried overnight and is directly pressed into tablets as indicated in Example 1.

3. Oral Spray

Gallopamil hydrochloride		1.0 g
Ethanol		8.0 g
Methyl cellulose		0.3 g
Polyoxyethylene sorbitan monolaurate		0.3 g
Peppermint oil		0.5 g
Res. water	ad	100.0 g

Gallopamil hydrochloride is dissolved in the mixture of ethanol/water, the mentioned monolaurate and peppermint oil are added. The solution is filtered and filled into 20 ml glass bottles. The bottles are closed with a dosing pump (spray pump).

4. Oral Spray

Verapamil hydrochloride	2.0 g
Ethanol	11.0 g
Methyl cellulose	0.3 g
Polyoxyethylene sorbitan monolaurate	0.4 g
Peppermint oil	0.6 g

Res. water	ad	100.0	g

For preparation see Example 3. /14

5. Nasal Spray

Verapamil hydrochloride		0.8	g
Sodium hydrogen phosphate		0.1	g
Sodium chloride		0.7	g
Methyl cellulose		0.1	g
Benzalconium chloride		0.01	g
Res. water	ad	100.0	g

Methyl cellulose and benzalconium chloride are dissolved in part of the water, the other components are dissolved in the rest of the water. Both solutions are joined and filled into spraying bottles made from polyethylene.

6. Sniffing Powder

Gallopamil hydrochloride		1.5	g
Peppermint oil		0.1	g
Lactose	ad	100.0	g

Gallopamil hydrochloride and lactose are mixed and finely ground on a suitable mill. The peppermint oil is admixed by spraying. The mixture is sifted and filled into a dosing dispenser.

Example 7

Application

6 healthy test persons (2 women and 4 men) aged between 24 and 46 years, whose blood count, liver enzymes, volatile urine substances, and electrolyte status were within normal ranges, were administered respectively a sublingual tablet with 20 mg of verapamil and at intervals of at least 1 week an oral tablet /15 with 80 mg of verapamil. The test subjects did not take any other medications or alcohol before and during the testing period. They were instructed to place the tablets under the tongue, to move it slightly, and if possible swallow as little saliva as possible.

In the peroral application (p.o.) was reached the maximum mean serum concentration of 125.6 mg/ml after an average of 80 minutes; the half lives amounted to 0.95 hours for the distribution phase and to 6.08 hours for the elimination phase. After the sublingual application, the highest serum concentration in the medium amounted to 26.0 mg/ml and was reached after an average of 71.7 minutes. For the distribution phase was found a half life of 0.73 hours and for the elimination phase a half life of on average 4.39 hours. A latency time until the appearance of the substance in the serum of 18.4 minutes was determined for the p.o. administration and of 0.8 minutes for the sublingual administration. The relative

bioavailability of verapamil (p.o. = 1.0) amounted on average to 2.7.

There was a close correlation between the serum concentration and the PQ time extension. In order to achieve the same PQ time extensions in the p.o. administration are required about 3 times higher serum concentrations than after sublingual administration. The sublingual application of verapamil decreases the range of all the important pharmacokinetic parameters in comparison to the p.o. administration. Thus, the variation coefficient for the maximum serum concentration value in the sublingual administration amounted to 49.7% in comparison with 120.6% in the p.o. administration. For the time until the maximum value is reached it is 25.0% (p.o. 54.7%) and for the elimination half life it is 26.4% (p.o. 68.9%).